COVID-19 Therapeutics Outcome: Systematic Review and Data Analysis

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Abstract

Background: Several medications already placed in the world therapeutic guidelines for coronavirus disease 2019 (COVID-19) were given to affected patients and produced positive and negative outcomes.

Aims of the study: This review evaluated therapeutic outcomes (recovery and mortality) used for COVID-19 patient management in clinical settings since the emergence of SARS-CoV-2 the causative agent of (COVID-19).

Method: The PRISMA-P and PRISMA statements were used to facilitate the development and reporting of this systematic review. Included articles were full-text articles, written in English and published in peer-reviewed journals from March 26, 2020. Recent eligible systematic review articles were also included for interpretation and analysis. Data were reported as percentage changes compared to the total number of patients in each study. For each drug, the proportion of positive outcomes were compared to the proportion of negative outcomes using a z-test ($p < 0.05$) to determine statistical significance.

Results: The total number of eligible studies included in this review was 69, and 48 different therapeutics were reported. The data analysis showed positive outcomes for COVID-19 patient treatments using hydroxychloroquine (66.6%), azithromycin (55.5%), lopinavir/ritonavir (54.9%), systemic corticosteroids (52%), umifenovir (51.2%), interferon (50%), remdesivir (45.9%), Ribavirin (43.5%), moxifloxacin (35.3%) and oseltamivir (33.6%). Negative outcomes were related mainly to systemic corticosteroids (21.3%), followed by remdesivir (16.9%), moxifloxacin (13.4%) and oseltamivir (12.5%). However, when comparing the proportions of positive outcomes to negative outcomes for reported drugs, the only statistically significant outcomes were observed among the hydroxychloroquine ($p < 0.05$) treatment group.

Conclusion: This study systematically reviewed 69 research articles linking therapies to clinical outcomes for COVID-19 patients. This review has provided insight into recovery and mortality outcomes associated with available COVID-19 therapeutic options. Data analysis showed positive outcomes for COVID-19 patient treatments primarily with hydroxychloroquine, azithromycin and lopinavir/ritonavir.

Introduction

In the absence of any approved treatment and vaccination for COVID-19 patients (1, 2), healthcare providers, scientists and researchers are working together to establish an efficient pharmacological treatment and vaccination that could end the spread of the disease. People all over the world have been affected negatively by COVID-19, and Table 1 (showing data from April 20, 2020) indicates that developed countries with the best healthcare systems have been affected the most; those countries have the highest mortality and morbidity rates (3).

On April 20, 2020, there were 2,423,498 COVID-19 cases worldwide with remarkably high patient recovery rates in Germany (62.7%) and Spain (40.2%) compared to the US (9.3%) and other European countries, save the UK where no data has been published on COVID-19 recovery (3). Recoveries differ among most European countries despite consistent treatment protocols, which include remdesivir, lopinavir/ritonavir, hydroxychloroquine, chloroquine, interferon beta and monoclonal antibodies (4). Early diagnosis and therapeutic intervention have had positive effects on patient recovery while prolonged hospital stays have increased hospital-acquired infection risks and bed occupancies. Other factors (such as age, ethnicity, gender and income) have varied impacts on patient discharge and recovery rates (4, 5).

Since the emergence of COVID-19, several therapeutics (such as hydroxychloroquine, chloroquine, remdesivir, interleukin-6 pathway inhibitors and convalescent plasma therapy) have been updated and included in global therapeutic guidelines for COVID-19 depending on in vitro or extrapolated and clinical evidence in patients diagnosed with Ebola, severe acute respiratory syndrome coronavirus (SARS-CoV) and *Middle East Respiratory Syndrome* coronavirus (MERS-CoV), producing positive outcomes among affected (1,2, 6).

The US Food and Drug Administration (FDA) has permitted emergency usage of two antibiotics (hydroxychloroquine-chloroquine and convalescent plasma therapy) to be tested on COVID-19 patients (7,8).

Despite lacking exact therapeutic guidelines for COVID-19 patient treatment, a study was conducted to determine the most applicable guidelines by using a panel of experts from 12 countries who endorsed many questions regarding ICU care of COVID-19 (10). The recommendations generated attempted to balance benefit and harm, resource and cost implications as well as equity and feasibility. However, in the absence of conclusive evidence, the results provided suggestions against the use of systematic corticosteroids, empiric antimicrobial agents, intravenous immunoglobulin, convalescent plasma, lopinavir/ritonavir and interferon, which are often combined with Ribavirin therapy, hydroxychloroquine, chloroquine or tocilizumab for COVID-19 management (9).

Of note, the first systematic review of the therapeutic management of COVID-19 patients reported that corticosteroid was most commonly mentioned in selected COVID-19 research, followed by antiviral medications lopinavir, oseltamivir and arbidol hydrochloride (7), however, the authors concluded that the majority of the stated articles in the review were of low quality with conflicting and incomplete designs and outcomes (7). Hence, clarifying effective and safe treatments remains challenging despite multiple published COVID-19 studies appearing daily (1, 2, 6, 9).

In this review, we followed Tobaiqy et al.'s (1) lead by using a similar search protocol on defined published articles to identify relevant articles on COVID-19 patient therapeutics and to assess the treatments' outcomes.

Methods

The PRISMA-P and PRISMA statements (10) were used to improve the reporting of this systematic review.

Inclusion criteria

Relevant articles (full-text, English and peer-reviewed articles published from March 26 to April 13 of 2020) were found in the PubMed and ScienceDirect electronic databases. A published systematic review by the research team (1) was also screened for eligible articles containing defined COVID-19 treatment outcomes that included recovery and mortality data.

Exclusion criteria

Duplicate articles were identified by the two researchers (SA and AM) and eliminated. Titles with abstracts were screened independently by the same researchers for inclusion criteria. For articles of uncertain value, the full text was checked. Disagreements between two reviewers after full text screening were reconciled via consensus by *a third reviewer (MT)*. All articles were documented according to the PRISMA guidelines presented in the form of a PRISMA flow diagram (10), and thorough explanations were documented for inclusions and exclusions. A quality assessment of the studies was undertaken based on Care Guidelines (Equator Network) (11). Critical appraisal checklists applicable to each study design were applied and checked by a second reviewer. Publication bias and quality issues were considered before conducting a quantitative meta-analysis and meta-narrative.

The checklist tool used to extract data was designed to focus on the population, methodology, specific mention of clinical findings, therapeutic interventions, follow-up and outcomes. Ethical review was not required due to the nature of this study.

The combination of the search keywords included "SARS-COV-2", "COVID-19", "clinical trial", "case report", "case series", "prospective study", "retrospective study", "cohort study", "antibacterial", "antiviral" and "convalescent plasma". The inclusion criteria set no study design restrictions, focusing on therapeutics used for COVID-19 patient treatment and corresponding outcomes. The objectives of this research were:

- (1) Identify different types of COVID-19 therapeutics used in clinical settings from March 26, 2020, to April 13, 2020; and
- (2) Evaluate clinical outcomes of COVID-19 treatments for recovery and mortality rates.

Data were reported as percentage changes compared to total patient numbers in each study. Therapeutic outcomes were measured according to patient discharge, recovery, ongoing hospitalization and mortality rates. Patient hospitalization discharges due to recovery were considered positive outcomes, while mortality was defined as a negative outcome.

For each drug, the proportion of positive outcomes was compared to the proportion of negative outcomes using a z-test ($p < 0.05$) to determine statistical significance. The statistical analyses were performed using Prism-V software (La Jolla, CA, USA).

Results

Forty-one articles were identified by the previous systematic review, and 39 were included by following CARE guidelines. As of April 13th, 2020, 326 initial manuscripts were identified from the PubMed ($n = 193$) and ScienceDirect ($n = 133$) databases. All articles were documented according to the PRISMA guidelines and presented in the form of a PRISMA flow diagram (Figure 1) with exclusions documented as follows: duplicates removed ($n = 55$), records screened ($n = 271$), records excluded ($n = 48$) including nine incomplete articles, language ($n = 20$ with 14 Spanish, 2 French, 4 Chinese articles) and outside the period of investigation ($n = 19$).

Of the full-text articles assessed for eligibility ($n = 223$), 193 articles were excluded for the following reasons: no therapeutics data ($n = 88$), review articles ($n = 59$), commentary ($n = 35$) and incomplete data ($n = 11$). That left 30 articles for review and analysis. A consensus was reached for those studies to be included ($n = 69$) without the need for a third reviewer. As seen in Figure 1, the previous systematic review produced 39 of these articles and the current study produced 30 articles (references from 12-80).

Reported Therapeutics

Forty-eight different therapeutics were reported in this review, an average of 4.4 therapeutic per study (Tables 2 and 3). The anti-inflammatory medication corticosteroid ($n = 50$), under different names and product characteristics, was the most frequently reported clinical therapy for COVID-19 management, followed by the antiviral HIV medication lopinavir/ritonavir ($n = 35$), interferon ($n = 30$), oseltamivir ($n = 28$) and umifenovir (arbidol hydrochloride; $n = 26$). Among the antibacterial medicines, moxifloxacin ($n = 11$), azithromycin ($n = 7$) and hydroxychloroquine ($n = 7$) were the most reported.

Therapeutic Outcomes

The data analysis (Tables 3 and 4) showed positive COVID-19 patient treatment outcomes with hydroxychloroquine (66.6%), azithromycin (55.5%), lopinavir/ritonavir (54.9%), systemic corticosteroids (52%), umifenovir (51.2%), interferon (50%), remdesivir (45.9%), Ribavirin (43.5%), moxifloxacin (35.3%) and oseltamivir (33.6%). Available data is shown in (Figure 2).

Negative outcomes were related mainly to systemic corticosteroids (21.3%), remdesivir (16.9%), moxifloxacin (13.4%), oseltamivir (12.5%), lopinavir/ritonavir (12.3%), umifenovir (12.2%) and interferon (10.8%). However, when comparing positive and negative outcome proportions, the only statistically significant outcomes were observed among the hydroxychloroquine treatment group (Table 4).

Discussion

This study was conducted based on recently published studies considering therapeutics used to treat COVID-19. From the emergence of this novel coronavirus to April 13, 2020, 69 research articles on COVID-19 have been published that were deemed suitable for inclusion in this systematic study. Most of these articles were case reports, case series or prospective and retrospective empirical research. The primary objective of this systematic review was to assess COVID-19 therapeutic outcomes in the defined populations irrespective of age or severity of the disease from the published articles. The data analysis showed statistically significant positive treatment outcomes with hydroxychloroquine (66.6%) only. Kaletra® (lopinavir/ritonavir) also resulted in positive patient treatment outcomes (54.9%) but was not considered statistically significant.

Chloroquine phosphate and hydroxychloroquine showed favourable recovery outcomes in several reports (Table 3). A small open label and non-randomized clinical trial (49) was initially useful, allowing some countries to start hydroxychloroquine trials and include it with therapeutics guidelines due to urgency and a lacking effective treatment. However, despite the study lacking a control group and randomization, it reported that hydroxychloroquine decreased viral loads in treating subjects (24). The effects of hydroxychloroquine were considerably more potent when administered with azithromycin according to clinical necessity (49). Another study could not confirm the benefits of chloroquine and hydroxychloroquine for COVID-19 patients even if other

medications were added, such as macrolides (81). However, healthcare providers noticed lower hospital stays and an increased frequency of ventricular arrhythmias when the drugs were administered to COVID-19 patients (81).

In this systematic review, corticosteroids were the most commonly reported medicine, as was found in a previous report (1). The recommendations of the WHO and CDC about corticosteroid administration for COVID-19 patients was that they should not be used routinely for treatment of acute respiratory distress syndrome (ARDS) or viral pneumonia, due to an absence of conclusive scientific evidence (82). However, for patients with other underlying conditions, such as chronic obstructive pulmonary disease exacerbation and asthma, corticosteroids are allowed.

Several randomized controlled trials reported that systemic corticosteroids may decrease the duration of mechanical ventilation and the incidence of death for critically ill patients suffering from ARDS (83, 84)). Interestingly, this study found that corticosteroids had positive therapeutic outcomes in 52% of treated patients and the highest percentage of negative outcomes (21.3%) among patients. More results concerning corticosteroid treatment for COVID-19 is expecting following a clinical trial of methylprednisolone, where the primary outcome is to assess the incidence of treatment failure in 14 days (85).

The positive outcomes resulting from the use of umifenovir, Ribavirin, moxifloxacin and oseltamivir were 51.2%, 43.5%, 35.3% and 33.6%, respectively. Negative outcomes in this systematic review referred to mortality occurring during treatment for COVID-19 infection. The highest negative outcomes were associated with corticosteroids (21.3%), followed by remdesivir (16.9%), moxifloxacin (13.4%) and oseltamivir (12.5%).

Interferon was the third most commonly mentioned medicine in this review. It possesses antiviral activity that identifies groups of α , β , ϵ , ω and κ cytokines subtypes (86). The Chinese therapeutic guidelines recommend the use of Interferon-alpha via vapour inhalation in conjunction with ribavirin to treat COVID-19 patients (86). In this review, ribavirin to treat COVID-19 patients (86). In this review, interferon and ribavirin resulted in positive outcomes in 50% and 43.5% of patients, respectively.

Remdesivir was reported on four times in this review and resulted in positive outcomes for nearly 45.9% of patients (Table 3). Remdesivir was the first antiviral agent designed for the Ebola virus disease (86), demonstrating significant antiviral activity against several RNA viruses (87, 88). Several international clinical trials are presently evaluating remdesivir's therapeutic benefits and it has been suggested that comprehensively monitoring metabolic effects including liver enzymes (89) and complete blood counts is required, as this medication is not recommended for use with patients with abnormal glomerular filtration rates or using dialysis (90, 91).

In the US, remdesivir was the first treatment used for a confirmed COVID-19 patient as a compassionate therapeutic (51). The patient's clinical indications improved after a single day of use, as it can enhance lung function (51). However, the efficacy and protection of such antiviral agents requires further testing in clinical trials for COVID-19 administration.

The results of this systematic review and the outcome analysis should be interpreted with caution. As reported previously (1), most articles in this review were of low quality, with the designs and outcomes being incomplete or inconsistent with confounders. Hence, they are challenging to interpret regarding therapeutic efficacy and safety.

Despite these limitations, this review has provided insight into recovery and mortality outcomes associated with available COVID-19 therapeutic options. The major strength of this study is that it offers more in-depth knowledge about COVID-19 therapeutic outcomes in systematic manner, particularly in the absence of any conclusive evidence concerning the therapeutic management of COVID-19.

Conclusions

This study systematically reviewed 69 research articles linking therapies to clinical outcomes for COVID-19 patients. Data analysis showed patient recovery with treatments of hydroxychloroquine, azithromycin, lopinavir/ritonavir, systemic corticosteroids, umifenovir and interferon. Negative outcomes were predominantly associated with systemic corticosteroids, remdesivir, moxifloxacin and oseltamivir. However, when comparing positive outcomes and negative outcomes for each drug, the only statistically significant outcomes were observed among the hydroxychloroquine treatment group.

Declarations

Authors' Contributions

M.T conceived of the presented idea, M.T, N.H, M.M, S.A and A.M contributed to the design and implementation of the research, to the analysis of the results and to the writing of the manuscript. M.T supervised the project.

Availability of Data and Materials

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Conflicts of Interest

No conflicts of interest to declare.

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Tables

Table1: TheTherapeutic Guidelines and Recovery Rates among the DevelopedCountries, as of April 20th 2020

Country	TherapeuticTreatments	AffectedCases	RecoveryCases	RecoveryRate
Germany	Remdesivir, lopinavir/ritonavir,hydroxychloroquine, chloroquine, interferon beta, and monoclonalantibodies	145,743	91,500	62.7%
Spain		200,210	80,587	40.2%
USA	Hydroxychloroquine,Chloroquine Remdesivir Convalescent Plasma	764,265	71,012	9.3%
UK	Ivermectin Convalescent Plasma Lopinavir/ritonavir Tocilizumab hydroxychloroquinechloroquine ACE inhibitors	120,067	NA	NA

Table2: ReportedTherapeutics

	Therapy	Studies(n)
1.	Systemic Steroids	50
2.	Lopinavir + Ritonavir	35
3.	Interferon	30
4.	Oseltamivir	28
5.	Umifenovir	26
6.	Immunoglobulin / GammaGlobulin	21
7.	Ribavirin	14
8.	Moxifloxacin	11
9.	Azithromycin	7
10.	Hydroxychloroquine	7
11.	Ganciclovir	6
12.	Levofloxacin	5
13.	Chinese TraditionalMedicine	4
14.	Tocilizumab	4
15.	Remdesivir	4
16.	Linezolid	3
17.	Convalescent PlasmaTherapy	3
18.	Peramivir	3
19.	Tazobactam	3
20.	Amoxicillin	2
21.	Vancomycin	2
22.	Lopinavir	2
23.	Thymosin	2
24.	Thymalfasin	2
25.	Tigecycline	2
26.	Ceftazidime	2
27.	Chloroquine	2
28.	Favipiravir	2
29.	Meropenem	2
30.	Thalidomide	1
31.	Darunavir	1
32.	Zadaxin	1
33.	Caspofungin,	1
34.	Voriconazole	1
35.	Penicillin	1
36.	Imipenem/Cilastatin	1
37.	Teicoplanin	1
38.	Piperacillin	1
39.	Cefoperazone	1
40.	Cefoselis	1
41.	Thymopentin	1
42.	Ceftriaxone	1
43.	Sulbactam	1
44.	Ofloxacin	1
45.	Recombinant Cytokine Gene DerivedProtein	1
46.	Thymopentin	1
47.	Ceftriaxone	1
48.	Cefepime	1

Table 3: Therapeutics used forCOVID-19 patients and the outcomes in differentcountries

Consensus on final inclusion of studies (n=69)(negotiated without the need for a thirdreviewer).

Therapeutics	StudyLocation	StudyDesign	PatientsNumber (n)	Patients MeanAge (years)	ICU Admission	MechanicalVentilation	Recovery	Mortality	Reference
Hydroxychloroquine 14(100%)	France	Prospective	14	51.2	NA	NA	8 (57.1%)	NA	Gautret et al2020
Hydroxychloroquine 6(100%) Azithromycin 6(100%)	France	Prospective	6	51.2	NA	NA	6 (100%)	0	
Oseltamivir 18(100%) Antibiotics 18(100%) Corticosteroid 11(61.1%)	China	Retrospective	18	NA	18 (100%)	6 (33.3%)	NA	17 (94.4%)	Cao J. et al 2020
Favipiravir 116(100%)	China	Prospective	116	NA	NA	21 (18.10%)	71 (61.20%)	NA	Chen et al 2020
Umifenovir 120(100%)	China	Prospective	120	NA	NA	27 (22.50%)	62 (51.67%)	NA	
Interferonα-1b Amoxicillin	China	Casereport	1	55-day-old	1 (100%)	1 (100%)	1 (100%)	0	Cui Y. et al2020
Vancomycin Remdesivir	USA	Casereport	1	35-year-oldman	0	1 (100%)	1 (100%)	0	Holshue et al2020
Oseltamivir 38(93%) Antibiotics 41(100%) Corticosteroid 9(22%)	China	Prospective	41	49	13 (32%)	12 (29%)	28 (68%)	6 (15%)	Huang C. et al2020
Umifenovir50(83.3%) Lopinavir +Ritonavir 41(68.3) Interferon 12(20%) Ribavirin 7(11.7%) Oseltamivir 2(3.3%) Glucocorticoid34(56.7%) Immunoglobulin 28(46.7%) Antibiotic therapy 56(93.3)	China	Retrospective	60 severecases	57 Range (26-97)	52 (86.6%)	9 (15%)	2 (3.3%)	0	Huang M. et al2020
Lopinavir +Ritonavir 99(100%)	China	Prospective	99	58 Range (49-68)	NA	10 (10.1%)	78 (78.8%)	19 (19.2%)	Cao B. et al2020
Thalidomide Methylprednisolone Ofloxacin Oseltamivir Lopinavir +Ritonavir	China	Casereport	1	45-year-oldwoman	1 (100%)	1 (100%)	1 (100%)	0	Chengshui Chen2020
Lopinavir +Ritonavir Umifenovir 249(100%) Corticosteroid(22%)	China	Retrospective	249	51	22 (8.8%)	NA	215 (86.3%)	2 (0.8%)	Jun Chen et al2020
Oseltamivir, Ganciclovir,Lopinavir + Ritonavir 75(76%) Antibiotics 45(45%) Glucocorticoid 19(19%)	China	Retrospective	99	55.5	2 (2%)	17 (16.8%)	31 (31%)	11 (11%)	Chen N et al2020

Immunoglobulin 27(27%)									
Lopinavir + Ritonavir 221(75.9%) Interferon α 2b 132(45.4%) Recombinant cytokine gene-derived protein 55 (18.9%) Umifenovir 50(17.2%) Chinese Medicine 281(96.6%) Glucocorticoids 67(23%) Oseltamivir 1(0.3%) Chloroquine 2(0.7%)	China	Retrospective	291	46	NA	NA	159 (54.6%)	2 (0.7%)	Chen X et al 2020
Antibiotics 637(58.0%) Oseltamivir 393(35.8%) Antifungal 31(2.8%) Glucocorticoids 204(18.6%)	China	Retrospective	1099	47	55 (5.0%)	67 (6.1%)	64 (5.8%)	15 (1.4%)	Guan W. et al 2020
Antivirals 329(77%) Antibiotics 239(56%) Glucocorticoids 119(28%) Immunoglobulin 68(16%)	China	Retrospective	450	NA	NA	95 (21.1%)	195 (43.3%)	35 (7.6%)	Liang B et al 2020
Oseltamivir 7(13.7%) Interferon 51(100%) Lopinavir + Ritonavir 51(100%) Thymopentin 48(94.1%) Traditional Chinese medicine	China	Retrospective	51	45	7 (13.7%)	6 (11.7%)	50 (98%)	1 (1.9%)	liu lei and Gao Jian-ya 2020
Antiviral 46(100%) Antifungal 5(10.9%) Budesonide 2(4.4%) Interferon alpha 43(93.5%)	China	Retrospective	46	22.5 Range (10-35)	9 (20%)	9 (20%)	36 (78.3%)	0	Liao J et al 2020
Lopinavir +Ritonavir Azithromycin Ceftriaxone Tazobactam Levofloxacin	South Korea	Casereport	1	54-year-oldman	0	0	1 (100%)	0	Lim J et al 2020
Lopinavir 10(100%) Interferon α 2b 10(100%) Immunoglobulin 2(20%) Methylprednisolone 2(20%)	China	Retrospective	10	42 Range (34-50)	3 (30%)	5 (50%)	7 (70%)	0	Liu F et al 2020
Antibiotic 55(86%) Antiviral 64(100%) Traditional Chinese medicine 13 (20%) Immunoglobulin 23(36%) Thymosin 33(52%)	China	Retrospective	64 Medical staff	35	0	0	34 (53%)	0	Liu J et al 2020

corticosteroids 7(11%)									
Ribavirin 1(16.6%) Oseltamivir 6(100%) Glucocorticoids4 Immunoglobulin 1(16.6%)	China	Retrospective	6	3 Range (1-7)	1 (16.6%)	1 (16.6%)	6 (100%)	0	Liu W et al2020
Antibiotics 106(97.2%) Antivirals 107(98.2%) Glucocorticoid therapy 72(66.1%) immunoglobulin 61(56.0%)	China	Retrospective	109	55	NA	28 (25.7%)	78 (71.6%)	31 (28.4%)	Liu Y et al 2020
Lopinavir + Ritonavir 10(100%) Antibiotics 10(100%) Interferon 3(30%) Methylprednisolone 3(30%)	China	Retrospective	10	54 Range (27 -64)	0	0	5 (50%)	0	Lo IL et al2020
Lopinavir + Ritonavir 27(17.4%) Umifenovir 31(20.0%) Interferon 30(19.4%) Thymalfasin 11(7.1%) Immunoglobulin 9(5.8%) Corticosteroid 79(51%) Immune enhancer 14(9%)	China	Retrospective	155	54 Range (42-66)	NA	36 (23.2%)	70 (45.2%)	22 (14.1%)	Mo P et al2020
Oseltamivir 124(89.9%) Moxifloxacin 89(64.4%) Ceftriaxone 34(24.6%) Azithromycin 25 (18.1%)Glucocorticoid 62 (44.9%)	China	Retrospective	138	56 Range (22-92)	36 (26.1%)	32 (23.1%)	47 (34.1%)	6 (4.3%)	Wang D et al 2020
Umifenovir 36(100%) Antibiotic therapy 66(98.5%) Corticosteroids 10(14.9%)	China	Retrospective	36	42 Range (35-62)	NA	NA	12 (33%)	0	Wang Z et al2020
Antibiotic therapy 66(98.5%) Corticosteroids 10(14.9%)	China	Retrospective	31	42 Range (35-62)	NA	NA	6 (19%)	5 (16%)	
Antibiotics 185(98.4%) Antiviral drugs 158(84.0%) Corticosteroids 59(31.4%)	China	Retrospective	188	51.9 Range (21-83)	50 (26.6%)	NA	145 (77.1%)	43 (22.9%)	Wu C et al 2020
Oseltamivir Cefoselis Glucocorticoid	China	Casereport	1	41-year-oldman	1 (100%)	1 (100%)	1 (100%)	0	Wu F et al 2020
Oseltamivir 38(55.1%) Moxifloxacin, Ceftriaxone,Azithromycin, Tigecycline Linezolid 31(44.9%)	China	Retrospective	69	57 Range	NA	5 (7.2%)	4 (5.8%)	1 (1.5%)	Xu Y et al 2020

Methylprednisolone 6(8.7%)				(43-69)					
Oseltamivir 45(100%)	China	Retrospective	45	56.7	7	26	11	1	Xu Y et al 2020
Ribavirin 45(100%)					(15.5%)	(57.7%)	(24.4%)	(2.2%)	
Antibacterial agents 45(100%)									
Antifungal agents 19(42.2%)									
Convalescent plasma 6(13.3%)									
Glucocorticoids 21(46.7%)									
Immunoglobulin 28(62.2%)									
Albumin 35(77.8%)									
Interferon alpha 8(13%)	China	Retrospective	62	41	1	1	1	0	Xu XW et al2020
Lopinavir+ Ritonavir 4(6%)					(1.6%)	(1.6%)	(1.6%)		
Umifenovir + Interferon 1(2%)									
Lopinavir+ Ritonavir +Interferon 21 (34%)									
Umifenovir + Lopinavir +Ritonavir 17 (28%)									
Umifenovir + lopinavir +Ritonavir + Interferon 4(6%)									
Antibiotics 28(45%)									
Corticosteroid 16(26%)									
Gamma globulin 16(26%)									
Methylprednisolone	China	Casereport	1	50-year-oldman	1	0	0	1	Xu Z et al2020
Moxifloxacin					(100%)			(100%)	
Lopinavir +Ritonavir									
Interferonalfa-2b									
Meropenem									
Oseltamivir18(35%)	China	Retrospective	52	59.7	52	37	8	32	Yang X et al2020
Ganciclovir 14(27%)					(100%)	(71%)	(15.3%)	(61.5%)	
Lopinavir 7(13.5%)									
Antibacterial 49(94%)									
Glucocorticoids 30(58%)									
Immunoglobulin 28(54%)									
Oseltamivir, Umifenovir,Interferon, Lopinavir + Ritonavir 196(88.7%)	China	Retrospective	221	55	44	53	42	12	Zhang G et al 2020
Glucocorticoid 115(52%)					(19.9%)	(23.9%)	(19.0%)	(5.4%)	
Antibiotics 73(91.25%)	China	Retrospective	80	53	3	8	47	0	Zhang JC et al 2020
Oseltamivir 20(25%)					(3.75%)	(10%)	(58.75%)		
Ribavirin, ganciclovir orPeramivir 47 (58.75%)									
Umifenovir 49(61.25%)									
Antifungal 10(12.50%)									
Immunoglobulin 36(45%)									
Corticosteroids 29(36.25%)									
Interferon 70(87.50%)									
Lopinavir + Ritonavir5(6.25%)									
Antibiotics 181(95%)	China	Retrospective	191	56	50	58	137	54	Zhou F et

Lopinavir + Ritonavir 41(21%) Corticosteroids 57(30%) Immunoglobulin 46(24%)					(26%)	(30.3%)	(71.7%)	(28.2%)	al2020
Lopinavir + Ritonavir 16(80%) Umifenovir 13(65%) Interferon 5(25%) Ribavirin 1(5%) Antibiotic therapy 17(85%) Glucocorticoids 5(25%) Immunoglobulin 6(30%) Thymosin alpha1 4(20%) Chinese traditional medicine20 (100%)	China	Retrospective	20	43.2	1 (5%)	2 (10%)	14 (70%)	0	Ziying Lei et al2020
Umifenovir 3(100%) Methylprednisolone 1(33.3%) Ribavirin 2(66.6%) Immunoglobulin 1(33.3%) Moxifloxacin 3(100%) Oseltamivir 2(66.6%) Azithromycin 1(33.3%)	China	CaseReport	3 Familymembers	Father Kidney transplantrecipient 49 Mother49 Son24	1 (33.3%)	1 (33.3%)	3 (100%)	0	Song Chen et al 2020
Umifenovir 16(100%) Lopinavir + Ritonavir 16(100%) Immunoglobulin 11(68.8%) Corticosteroid 1 (6.2%) Antibacterial agents 9(56.3%)	China	Retrospective	16	41.8	Patients who need ICUadmission were excluded from study	Patients who need MV wereexcluded from study	15 (94%)	NA	Lisi Deng et al2020
Lopinavir + Ritonavir 17(100%) Immunoglobulin 13(76.5%) Corticosteroid 7(41.2%) antibacterial agents 12(70.6%)	China	Retrospective	17	47.25	Patients who need ICUadmission were excluded from study	Patients who need MV wereexcluded from study	9 (52.9%)	NA	
Lopinavir + Ritonavir 34(100%) interferon- 2b(100%)	China	Retrospective	34	40.5	NA	NA	19 (55.9%)	NA	Zhen Zhu et al2020
Umifenovir 16(100) interferon- 2b(100%)	China	Retrospective	16	26.5	NA	NA	16 (100%)	0	Haiyan Qiu et al2020
Interferon alfa 36(100%) Lopinavir + Ritonavir 14(39%)	China	Retrospective	36	8.3 Range (0-16)	0	0	36 (100%)	0	
Hydroxychloroquine 79(93.7%) Azithromycin 79(93.7%) Ceftriaxone 6(7.5%) Immunosuppressive 4(5%) NSAIDs 2(2.5%)	France	Prospective	80	52.5	3 (3.8%)	12 (15%)	65 (81.3%)	1 (1.2%)	Philippe Gautretet al 2020

Corticosteroid 107(52.7%) Umifenovir 47(23.2%) Lopinavir + Ritonavir 36(16.1%) Interferon alfa 48(23.6%) Thymalfasin 16(7.9%) Immunoglobulin 11(5.4%)	China	Retrospective	203	54	NA	39 (19.2%)	177 (87.1%)	26 (12.8%)	TieLong Chen et al2020
Lopinavir + Ritonavir 34(100%) Antibiotic therapy 34(100%) Glucocorticoid 16(47.1%) Immunoglobulin 14(41.2%)	China	Retrospective	34 Undergoing surgeries duringCOVID-19 infection	55	15 (44.1%)	12 (35.2%)	27 (79.4%)	7 (20.6%)	ShaoqingLei et al2020
Oseltamivir, Umifenovir,Lopinavir + Ritonavir 236(86%) Glucocorticoid 217(79%) Antibiotics 249(91%) Immunoglobulin 54(20%) Interferon 89(32%)	China	Retrospective	274	62	NA	119 (43%)	161 (58.7%)	113 (41.2%)	Tao Chen et al2020
Moxifloxacin 148 (65.78%) Ribavirin 71 (31.56%) Umifenovir 133(59.11%) Oseltamivir 138 (61.33%) Methylprednisolone 100(44%)	China	Retrospective	225	50	NA	NA	20 (8.8%)	2 (0.89%)	Ruoqing L et al2020
Antiviral treatment 78(91.8%): Umifenovir 51(60%) Lopinavir + Ritonavir 11(12.9%) Oseltamivir 9(10.6%) Paramivir 6(7.1%) Ganciclovir 5(5.9%) Ribavirin 4(4.7%) Meropenem 38(44.7%) Imipenem/cilastatin 1(1.2%) Moxifloxacin 40(47.1%) Levofloxacin 4(4.7%) Linezolid 18(21.2%) Vancomycin2(2.4%) Teicoplanin 2(2.4%) Tigecycline 2(2.4%) Piperacillin/Tazobactam 9(10.6%) Ceftriaxone sodium 3(3.5%) Cefoperazone/sulbactam 2(2.4%) Ceftazidime tazobactam 2(2.4%) Glucocorticoids 65(76.5%) Interferon 33(38.8%)	China	Retrospective	85 Fatalcases	65.8	NA	79 (93%)	0	85 (100%)	Yingzhen Du etal

Immunoglobulin therapy 38(44.7%)									
Carbapenem antibiotic 4(12%) Cephalosporins 7(21%) Macrolide antibiotic 18(55%) Penicillin antibiotic 23(70%) Other antibiotic 2(6%) Dexamethasone 28(85%) Lopinavir + Ritonavir 27(82%) Hydroxychloroquine 26(79%) Tocilizumab 4(12%)	Italy	Prospective	33	64 Range (59 -72)	33 (100%)	20 (60.6%)	9 (27.2%)	1 (3%)	Simone Piva et al2020
Interferon-a2b 42(62.7%) Ganciclovir 24(32.9%) Lopinavir + Ritonavir 61(83%) Oseltamivir 34(46.6%) Chinese traditional medicine20 (27.4%) Glucocorticoid 58(79.5%) Immunoglobulin 43(58.9%)	China	Retrospective	73	67	NA	22 (30.1%)	26 (35.6)	21 (28.8)	Xiao Tang et al2020
Moxifloxacin Lopinavir +Ritonavir	China	Casereport	1	50-years-old haemodialysispatient	NA	NA	1	0	Bin Tang et al 2020
Remdesivir 7(29.1%) Hydroxychloroquine 1(4.1%) Lopinavir + Ritonavir 1(4.1%)	USA	Retrospective	24	64 Range (23-97)	24 (100%)	18 (75%)	5 (21%)	12 (50%)	Pavan K et al2020
Lopinavir + Ritonavir,Oseltamivir, Umifenovir, Interferon 125(100%) Antibiotic therapy 79(63.2%) Glucocorticoids 35(28.0%) immunoglobulin 24(19.2%)	China	Retrospective	125	38.76	19 (15.2%)	4 (3.2%)	47 (37.6%)	0	Ruirui Wang et al2020
Corticosteroid 64(56.6%) Umifenovir 55(48.7%) Ribavirin 19(16.8%)	China	Retrospective	113	52 Range (43-63)	NA	18 (15.9%)	69 (61.1%)	2 (1.8%)	Kaijin Xu et al2020
Ceftriaxone Amoxicillin/clavulanate	Taiwan	Casereport	1	55-year-oldwoman	0	0	1 (100%) without antiviraltreatment	0	Shao-Chung Chenget al 2020
Moxifloxacin Umifenovir Tocilizumab	China	Casereport	1	60-year-oldman With multiplemyeloma	1	0	1 (100%)	0	Xuhan Zhang et al2020
Oseltamivir Hydroxychloroquine Lopinavir +ritonavir	Iran	Casereport	1	44-year-oldmale	NA	NA	NA	0	Ali Asadollahi- Amin et al2020

							the patient became asymptomatic after treatment with Lopinavir +ritonavir		
Trimethoprim/sulfamethoxazole Moxifloxacin Lopinavir +ritonavir Gamma-globulin	China	Case Report	1	29-years-old male	NA	NA	1 (100%)	0	Ling Ning et al 2020
Interferon 7(88%) Lopinavir + ritonavir 7(88%) Ribavirin 2(25%) Oseltamivir 1(12.5%) Adenosine(12.5%) Umifenovir 1(12.5%) Levofloxacin 4(50%) Moxifloxacin 3(38%) Ceftazidime 1(13%)	China	Prospective	8	22 Range (16-23)	0	0	4 (50%)	0	Lei Huang et al 2020
Corticosteroids 341(62.2%) Lopinavir + Ritonavir 164(29.9%) Umifenovir 401(73.2%) Oseltamivir 221(40.3%) Ribavirin 29(5.3%) Interferon α 168(30.7%) Immunoglobulin 213(38.9%)	China	Retrospective	548	60 Range (48-69)	NA	103 (18.7%)	287 (52.7%)	90 (16.5%)	Xiaochen Li et al 2020
Umifenovir 55(100%) Ribavirin 55(100%) Interferon- α 2b 55(100%) Traditional Chinese medicine 34 (61.8%) Methylprednisolone 21(38.1%)	China	Retrospective	55	59 Range (29-77)	NA	NA	45 (81.8%)	0	Changcheng Zheng et al 2020
Levofloxacin 17(35%) Ceftriaxone 22(46%) Azithromycin 10(21%) Linezolid 9(18.8%) other beta-lactams 15(31.3%) Lopinavir + Ritonavir 45(93.8%) Steroids 17(35.4%) Tocilizumab 2(4.2%) Chloroquine 45(93.8%) Interferon 41(85.4%)	Spain	Prospective	48	67 Range (53-74)	48 (100%)	45 (93.8%)	13 (27%)	6 (15%)	Helena Barrasa et al 2020 60
Interferon- α 1b 12(100%) Lopinavir + Ritonavir 8(66%) Ribavirin 2(16%)	China	Retrospective	12	14.5 Range (0.64-17)	0	NA	NA	0	Juan Chen et al 2020
Oseltamivir, Umifenovir, Ganciclovir,	China	Retrospective	204	49	NA	10	134	26	Ruyuan He et al 2020

Lopinavir, Ritonavir(98.53%) Moxifloxacin, Levofloxacin,Cephalosporins (97.02%) Albumin infusion(25.98%) Glucocorticoid(25.00%)				Range (34-62)		(4.90%)	(65.69%)	(12.75%)	
Hydroxychloroquine Tocilizumab	USA	Casereport	1 OnDurable LVADSupport	70-year-oldmale	1 (100%)	1 (100%)	0	1 (100%) patient developed severeARDS	Vinh Q et al 2020
Lopinavir + ritonavir 4(80%) Interferon alfa-1b 3(60%) Favipiravir 2(40%) Umifenovir 1(20%) Darunavir 1(20%) Convalescent plasma transfusion 5 (100%) methylprednisolone 5(100%)	China	Caseseries	5 Critically ill patients withsevere ARDS	Range (36-65)	5 (100%)	5 (100%)	3 (60%) Patients were on antiviralagents and improved after starting convalescent plasma transfusion	0	Chenguang Shen et al2020
Umifenovir 3(75%) Lopinavir+ Ritonavir 4(100%) Interferon 3(75%) Albumin, Zadaxin,Immunoglobulin, Antibacterial, Methylprednisolone, Oseltamivir,Casprofungin, Voriconazole 1(25%) Ribavirin 2(50%) Convalescent plasma 4(100%)	China	Casereports	4	Range (31-73)	3 (75%)	3 (75%)	3 (75%) Patients were on antiviralagents and improved after starting convalescent plasma transfusion	0	Bin Zhang et al2020
Oseltamivir or Peramivir 17(100%) Antibiotic 14(82.4%) Glucocorticoid 9(52.9%) The study done on H7N9patients not COVID- 19patients.	China	Prospective	17 H7N9patients	62.8	NA	14 (82.4%)	NA	3 (17.6%)	Chen J et al2020
Antibiotics 82(100%) Corticosteroids29(35.3%) Antivirals 82(100%)	China	Retrospective	82 Fatalcase	72.5	14 (17.1%)	33 (40.2%)	0	82 (100%)	Bicheng Zhang et al 2020
Remdesivir 53(100%) 40 (75%) received 10-daycourse 10 (19%) received 5-9- daycourse 3 (6%) less than 5-daycourse	USA 22 Japan 9 Italy12 Austria1 France4 Germany2 Netherlands 1 Spain 1Canada 1	Prospective	53	64 Range (23-82)	NA	30 (57%)	25 (47%)	7 (13%)	Jonathan Grein et al2020
Hydroxychloroquine Cefepime	USA	Casereport	1	40-year-old-male	1 (100%)	1 (100%)	After initiation ofRemdesiviris	0	Emily Hillaker etal 2020

Remdesivir							progressing toward discharge		
Methylprednisolone									

Table 4: Therapeutics used in COVID-19 and potential outcomes

Therapeutics	Number of patients(n)	Positive outcome(n)	Positive outcome%	Negative outcomes(n)	Negative outcomes%	P-value*
Hydroxychloroquine	129	86	66.6	3	2.3	0.006
Azithromycin	153	85	55.5	4	2.6	0.767
Lopinavir/Ritonavir	1881	1034	54.9	232	12.3	0.051
SystemicCorticosteroids	1897	986	52	404	21.3	0.237
Umifenovir	2161	1105.812	51.2	264.43	12.2	0.139
Interferon	1300	650.5	50	140	10.8	0.116
Remdesivir	62	28.47	45.9	10.5	16.9	0.072
Ribavarin	287	124.9	43.5	10.3	3.6	0.993
Moxifloxacin	516	182.3	35.3	69.36	13.4	0.362
Oseltamivir	1952	655.916	33.6	243.773	12.5	0.562

* For each drug, the proportion of positive outcomes were compared to the proportion of negative outcomes with a test of two proportions

Figures

Figure 1

PRISMA flow diagram

Figure 2

Therapeutics used in COVID-19 patients and potential outcomes